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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.				
10/511,691	10/14/2004	David Hands	20974YP	9304				
210 MERCK AND CO., INC P O BOX 2000 RAHWAY, NJ 07065-0907	7590 10/15/2007		<table border="1"><tr><td colspan="2">EXAMINER</td></tr><tr><td colspan="2">ANDERSON, REBECCA L</td></tr></table>		EXAMINER		ANDERSON, REBECCA L	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/511,691

Applicant(s)

HANDS ET AL.

Examiner

Rebecca L. Anderson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 August 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 15-27 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 15-27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 15-27 are currently pending in the instant application. Claims 15-27 are rejected.

Response to Amendment and Arguments

Applicant's amendment and arguments filed 21 August 2007 have been considered and entered into the application. As applicant has cancelled claims 1, 10, 13 and 14 and amended the independent claim 15 to require reacting the hydrochloride salt of a compound of formula 2 in the presence of an inorganic base and toluene, the 35 USC 102(b) rejection is withdrawn. Applicant has cancelled claims 1-14, however, the 35 USC 103(a) rejection is maintained for newly added claims 15-27.

In regards to the 35 USC 103(a) rejection, applicants' arguments have been fully considered but they are not persuasive. Applicants' argue that the Examiner has failed to demonstrate the specific motivation in U. S. Patent No. 5,719,147 that would have motivated one of ordinary skill in the art to prepare and utilize the subject compound in accordance with the claimed invention. This argument is not persuasive as KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness, KSR 82 USPQ2d at 1396.

Applicants' also argue that the Examiner has failed to establish a prima facie case of obviousness. Applicant argues that the '147 patent does not teach any of the following reaction conditions: It is noted that while the process of example 75 may not teach each and every one of the following reaction conditions, the '147 reference as a

whole does provide teaching and/or direction and motivation to each of these reaction conditions.

1) the temperature of the cyclization process; The prior art reference provides in example 75 that 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-(N-methylcarboxyacetamidrazono)morpholine (which corresponds to applicants formula 4) in 15ml of xylenes was heated at reflux for 2 hours. Heated at reflux in xylenes corresponds to applicants temperature of 140-150 degrees Celsius as can be seen in the CRC Handbook of Chemistry and Physics wherein the boiling points of the xylene solvents are 138, 139 and 144 degrees Celsius;

2) the use of the hydrochloride salt of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine; The prior art reference provides motivation to use the hydrochloride salt as the prior art reference as the prior art reference provides in another process of preparing substituted heterocycles of the structure as found on column 5, the use of an HCl salt and toluene, see example 101, column 131 wherein the hydrochloride salt of the product was broken by slurring in a mixture of toluene and sodium bicarbonate.

3) the use of toluene; The prior art reference provides motivation to toluene as the prior art reference as the prior art reference provides in another process of preparing substituted heterocycles of the structure as found on column 5, the use of an HCl salt and toluene, see example 101, column 131 wherein the hydrochloride salt of the product was broken by slurring in a mixture of toluene and sodium bicarbonate.

4) the use of an inorganic base (such as potassium carbonate); The prior art reference provides motivation to use an inorganic base as diisopropylethylamine is used in example 75 as the base, additionally, the prior art reference provides the use of appropriate bases to include diisopropylethylamine, potassium carbonate, sodium carbonate and the like on column 65 and utilizes the inorganic base of potassium carbonate in example 83, column 107 with the polar aprotic solvent of DMF.

5) the use of a polar aprotic solvent (such as dimethylsulfoxide or dimethylformamide); The prior art reference provides motivation to use a polar aprotic solvent as acetonitrile is used in example 75 as a polar aprotic solvent, additionally, the prior art reference provides the use of other polar aprotic solvents in the preparation of the substituted heterocycles of the structure as found on column 5, see example 83 wherein DMF is used; or

6) the use of an aqueous wash, such as with an aqueous salt solution, prior to conducting the cyclization. The prior art reference provides motivation to use an aqueous wash as the prior art provides washing with sodium bicarbonate in example 101, column 131.

Therefore, there would have been motivation and guidance in the '147 reference for one of ordinary skill in the art to have conducted the subject process in accordance with the claimed invention. As shown above, the Examiner has provided specific factual bases to support the assertion that the '147 patent would have motivated one of ordinary skill in the art to have conducted the subject process in accordance with the claimed invention.

Applicants' argue that there would have been no motivation in the '147 patent to conduct the cyclization process at a temperature of about 140-150 degrees Celsius in the absence of xylene and taught away from the present invention by suggesting that the solvent xylene would have been required. This argument is not persuasive as example 75 provides 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-(N-methylcarboxyacetamidrazono)morpholine (which corresponds to applicants formula 4) in 15ml of xylenes was heated at reflux for 2 hours. Heated at reflux in xylenes corresponds to applicants temperature of 140-150 degrees Celsius as can be seen in the CRC Handbook of Chemistry and Physics wherein the boiling points of the xylene solvents are 138, 139 and 144 degrees Celsius. Additionally, applicants' claimed invention does not exclude xylene solvents from the reaction.

Applicants' argues that there would have been no motivation in the '147 patent to use the hydrochloride salt of the compound and the reference teaches away from using the hydrochloride salt. This argument is not persuasive as it would have been obvious to one of ordinary skill in the art to use toluene and the HCl salt of the formula 2 when faced with the prior art reference as the prior art reference provides in another process of preparing substituted heterocycles of the structure as found on column 5, the use of an HCl salt and toluene, see example 101, column 131 wherein the hydrochloride salt of the product was broken by slurrying in a mixture of toluene and sodium bicarbonate.

Applicants' argue that there would have been no motivation in the '147 patent to use toluene rather than xylene and that the '147 patent teaches away from the present invention by suggesting that the solvent xylene would have been required. Again it is

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noted that applicants' instantly claimed invention does not exclude xylene solvents from the reaction. This argument is not persuasive as it would have been obvious to one of ordinary skill in the art to use toluene and the HCl salt of the formula 2 when faced with the prior art reference as the prior art reference provides in another process of preparing substituted heterocycles of the structure as found on column 5, the use of an HCl salt and toluene, see example 101, column 131 wherein the hydrochloride salt of the product was broken by slurrying in a mixture of toluene and sodium bicarbonate.

Applicants' argue that there would have been no motivation in the '147 patent to use an inorganic base, rather than the organic base N,N-diisopropylethylamine and that example 83 is not relevant. This argument is not persuasive as it would have been obvious to one of ordinary skill in the art to use an inorganic base other than diisopropylethylamine as the prior art reference provides the use of appropriate bases to include diisopropylethylamine, potassium carbonate, sodium carbonate and the like on column 65 and utilizes the inorganic base of potassium carbonate in example 83, column 107 with the polar aprotic solvent of DMF as the optimization of variables in a known process is prima facie obvious.

Applicants' argue that there would have been no motivation in the '147 patent to use a polar aprotic solvent rather than acetonitrile and teaches away from using other than acetonitrile. This argument is not persuasive as it would have been obvious to one of ordinary skill in the art to use a polar aprotic solvent other than acetonitrile, such as DMF as the prior art reference provides the use of both of these polar aprotic solvents in

the preparation of the substituted heterocycles of the structure as found on column 5, see example 83.

Applicants' argue that there would have been no motivation in the '147 patent to sue an aqueous wash prior to conducting the cyclization. This argument is not persuasive as it would have been obvious to one of ordinary skill in the art to wash the compound of the formula 4 with an aqueous phase, such as KCl, as the prior art provides washing with sodium bicarbonate in example 101, column 131 and the optimization of variables in a known process is prima facie obvious.

Applicants' argue that even if one of ordinary skill in the art would have been motivated to alter the process disclosed in the '147 patent, there would have been no direction in the '147 patent regarding which specific reagents, solvents, temperature, additional steps and/or other conditions should have been employed in the process. This argument is not persuasive for the reasons above which show that the '147 patent provides direction and motivation regarding the specific reagents, solvents, temperature, additional steps and/or other conditions to be employed to alter the process of example 75 in the '147 patent.

Lastly, applicants' argue that even if the Examiner has established a prima facie case of obviousness, the present invention provides unexpected results relative to the disclosure of U.S. Patent No. 5,719,147 as the present invention gives the desired compound in 85% yield (page 8, lines 8-9) which is unexpectedly higher than the yield disclosed for the procedure in the '147 patent (79% yield, example 75, column 104). This argument is not persuasive as applicant has not provided a showing as stated in

MPEP 716.02(a) and (b) that the results were greater than those which would have been expected from the prior art to an unobvious extent and that the results are of a significant, practical advantage. Specifically, any difference between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. The example in the specification (page 8, lines 8-9) and example 75 of the prior art reference does not discuss how or provide a showing that the differences in results are in fact unexpected an unobvious and of both statistical and practical significance. Applicant has the burden of explaining the data they provide as evidence of non-obviousness. Additionally, applicant has failed to provide a showing of sufficient scope as the example 1(pages 7 and 9) requires specific reaction conditions, such as, for example, the use of potassium carbonate, not just any inorganic base as claimed. Applicant has failed to provide a showing of sufficient scope, and failed to further show that the results are greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Maintained Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,719,147.

Determining the scope and contents of the prior art

US Patent No. 5,719,147 discloses substituted heterocycles of the structure as found on column 5 and their methods of preparation, columns 53-67. US Patent No. 5,719,147 discloses the stereochemistry of the compound corresponding to applicants' formula 1 on column 45, lines 45-60, which corresponds to the stereochemistry found in applicants' claims 26 and 27. This compound is prepared in example 75, column 104 from 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl

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morpholine (which corresponds to applicants formula 2) by the method of example 70, column 102 wherein 2(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl morpholine is reacted with N-methylcarboxy-2-chloroacetamidrazone and N,N-diisopropylethylamine in acetonitrile at room temperature for 20 hours. The organic layer was separated, dried over magnesium sulfate and concentrated in vacuo. Then 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-(N-methylcarboxyacetamidrazono)morpholine (which corresponds to applicants formula 4) in 15ml of xylenes was heated at reflux for 2 hours. Heated at reflux in xylenes corresponds to applicants temperature of 140-150 degrees Celsius as can be seen in the CRC Handbook of Chemistry and Physics wherein the boiling points of the xylene solvents are 138, 139 and 144 degrees Celsius.

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art and the claims at issue is that the prior art may differ: in the temperature of the cyclization (xylene solvents boiling points are 138, 139 and 144 degrees Celsius); by not using the hydrochloride salt of the compound of formula 2 and toluene (applicants' claims 15-27); by using diisopropylethylamine as the base instead of sodium carbonate, cesium carbonate, sodium hydroxide, potassium hydroxide and potassium carbonate (applicants' claims 24-25); by using acetonitrile as a polar aprotic solvent instead of dimethylformamide, dimethylsulfoxide (applicants' claims 17-18); or by not washing with an aqueous phase such as KCl, KHCO₃, K₂CO₃, Na₂CO₃, NaHCO₃ and NaCl (applicants' claims 19-22).

Resolving the level of ordinary skill in the pertinent art

However, it would have been obvious to one of ordinary skill in the art at the time of the invention, when faced with the prior art of US Patent No. 5,719,147, to prepare the compound of formula 1 as claimed as the prior art provides the cyclization of the compound of formula 4 in xylenes at reflux (the boiling point of xylenes are 138, 139 and 144). While one of the boiling points for xylene solvents is 144 which is within the ranges of 140-150 degrees Celsius, one be motivated by the expectation of additional methods to prepare compounds of the formula 1 by utilizing xylene which has a boiling point of 144 degrees Celsius or modifying the temperature from 138 and 139 degrees Celsius as the optimization of variables in a known process is prima facie obvious. It would have been obvious to one of ordinary skill in the art to use toluene and the HCl salt of the formula 2 when faced with the prior art reference as the prior art reference provides in another process of preparing substituted heterocycles of the structure as found on column 5, the use of an HCl salt and toluene, see example 101, column 131 wherein the hydrochloride salt of the product was broken by slurrying in a mixture of toluene and sodium bicarbonate. It would have been obvious to use base other than diisopropylethylamine as the prior art reference provides the use of appropriate bases to include diisopropylethylamine, potassium carbonate, sodium carbonate and the like on column 65 and utilizes the inorganic base of potassium carbonate in example 83, column 107 with the polar aprotic solvent of DMF as the optimization of variables in a known process is prima facie obvious. Additionally, it would have been obvious to use a polar aprotic solvent other than acetonitrile, such as DMF as the prior art reference

provides the use of both of these polar aprotic solvents in the preparation of the substituted heterocycles of the structure as found on column 5, see example 83. Lastly, the washing of the compound of the formula 4 with an aqueous phase, such as KCl would have been obvious as the prior art provides washing with sodium bicarbonate in example 101, column 131 and the optimization of variables in a known process is prima facie obvious.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday from 6:00am until 2:30pm.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

*/Rebecca Anderson/
Primary Examiner, AU 1626*

11 October 2007

Rebecca Anderson
Primary Examiner
Art Unit 1626, Group 1620
Technology Center 1600